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High-Flux and Low-Flux Membranes: Efficacy in Hemodialysis

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Background: Inadequacy of dialysis is one of the main causes of death in hemodialysis patients. Some studies have suggested that high-flux membrane improves the removal of moderate-sized molecules while other studies indicate no significant effect on them.
Objectives: This study aimed to investigate the dialysis efficacy of low-flux versus high-flux membranes in hemodialysis patients.
Patients and Methods: Forty hemodialysis patients participated in this cross-over clinical trial. Two sessions of low-flux and high-flux membrane dialysis were performed consecutively, in the first and second stage of the trial. In both stages, blood samples before and after the dialysis were taken and sent to the laboratory for assessment. Blood urea nitrogen (BUN), KT/V and the urea reduction ratio (URR) indexes were used to determine dialysis efficacy. Data were analyzed using t test and paired t test.
Results: The mean KT/V was 1.27 ± 0.28 in high-flux and 1.10 ± 0.32 in low-flux membrane which, these differences were statistically significant ($P = 0.017$). The mean of URR was 0.65 ± 0.09 in high-flux and 0.61 ± 0.14 in low-flux membrane, which these differences were not statistically significant ($P = 0.221$).
Conclusions: The high-flux membrane had better dialysis adequacy, so we suggest using high-flux membrane in hemodialysis centers.

*Keywords:*Hemodialysis; Dialysis Efficacy; High-Flux Membrane; Low-Flux Membrane; Iran

1. Background

Chronic Renal Failure (CRF) is a serious disorder. Four hundred thousand people are suffering from CRF in the United States of America. Its universal incidence is reckoned to be 260 million people every year with an increase rate of 6% (1). These people will need hemodialysis (HD), peritoneal dialysis or kidney transplant to continue their lives (2). There were 12500 patients under hemodialysis in Iran in 2006 (3). In spite of drastic advances in medical technology, the mortality rate of these patients has shown no meaningful decrease during the past 20 years and has been stabilized at 18% annually (4).

The principle of hemodialysis involves the clearance of solutes across a semi-permeable membrane through diffusion and ultrafiltration mechanisms. The utilized membranes are classified into two main groups: low-flux, which is based on using dialyzers with low permeability for water (5); and high-flux, non-celluloses membrane with increased permeability, which is capable of removing moderate-sized molecules between 10000 to 15000 Dalton, including many of the inflammatory proteins, $ß_2$ microglobulin and lipoproteins (6). Some studies have suggested that high-flux membrane improves the removal of moderate-sized molecules such as lipid profiles or homocysteine (7, 8) while other studies have concluded it has no significant impact on these molecules such as homocysteine levels (9).

Because of incomplete removal of uremic toxins, 90% of hemodialysis patients reveal symptoms of pathologic amyloidosis caused by $ß_2$ microglobulin after five years of dialysis (10). One of the most influential reasons to continue a certain treatment is the degree of its impact on the targeted disease; while, the inadequacy of dialysis has been recognized as a major reason for the mortality rate of the hemodialysis patients (11). If the efficiency of hemodialysis is not adequate, the level of blood toxins and the clinical symptoms of the patient are not controlled, which lead to either an increase in the duration of each dialysis session or the frequency of necessary dialysis per week. This will consequently increase the mortality and morbidity of the patients and the cost of dialysis (12, 13).

There are a number of factors, which influence the adequacy of the dialysis, such as the time of dialysis, the dialysate flow rate, the surface of dialyzer, and the blood flow rate. However, the employments of many of these factors are considered impossible, because they are neither beneficial, nor feasible. For example, increasing the duration of the dialysis over four hours is beyond the patient's tolerance and will increase the cost of dialysis to a large extent. Furthermore, increasing the dialysate flow rate do not have a significant effect on the adequacy of the dialysis (14).

With regard to the available capacity of the dialysis centers across the country and the increasing need for further facilities, it is clinically wise to limit the amount and time of dialysis to an optimal level. Therefore, reaching to certain level of dialysis adequacy is crucial, and it has led researchers to conduct some projects to obtain this adequacy. In spite of the emphasis on the employment of high-flux permeable membrane in the available research literature (15) and according to the crucial importance of using these membranes and the emphasis of the National Kidney Association of Iran on the necessity of these permeable membranes (16), there are still many wards utilizing low-flux permeable membranes (17). The contradictory results of the current published data prompted us to design this clinical trial study.

2. Objectives

This study was performed to compare the efficiency of low-flux versus high-flux membranes in patients who referred to dialysis center of the Shahid Beheshti Hospital in Hamadan city.

3. Patients and Methods

This research is a cross-over clinical trial study. Sample size was calculated based on a previous study in which House et al. (18) have studied the effect of high-flux vs. low-flux hemodialysis on homocysteine and lipids. Then 21 patients was estimated to be needed in each group based on the following parameters (β=0.20, α=0.05, σ1 (variance of homocysteine in high-flux group) = 1.925, σ2 (variance of homocysteine in low-flux group) =1.675, μ1 - μ2 (mean pre-dialysis homocysteine in high-flux group minus mean pre-dialysis homocysteine in low-flux group) = 2 (18). However, 40 patients were selected for more accuracy. From 114 patients who assessed for eligibility, 74 patients excluded because of not having the inclusion criteria (n = 32), occurrence of exclusion criteria (n = 22) or declined to participate (n = 20).

Inclusion criteria were as follows: participants' age between18 to 60 years, dialysis treatment for at least 6 months with conventional HD, using fistula or graft as vascular access, at least twice 4-hour dialysis session per week, consciousness for participation in study, hemoglobin $\geq$ 9 mg/dL, interdialytic weight gain less than 3 kg, not having any neoplasia.

Exclusion criteria were as follows: hypotension (systolic BP $\leq$ 90 mm Hg), acute clinical conditions (myocardial infarction, congestive heart failure, stroke, recent surgery, or severe sepsis) during the study, any vascular access dysfunction, discontinuation of dialysis less than 4 hours, reduction in patient's consciousness, patient's restlessness and agitation, severe nausea and vomiting during dialysis, starting other treatments.

During the research, the dialyzer was fixed and 500 mL/min bicarbonate solution was used as dialysate. The blood flow rate was fixed for each patient. Five thousand units of heparin per session as an anticoagulant were used. The sodium density of dialysate was 135 –145 meq/L with a stabilized temperature at 37°C. The amount of food and liquid taken for each participant throughout the study were the same and controlled. No blood transfusion was given to any patient during the study period.

3.1. Interventions and Comparison

In the first stage, all participants underwent dialysis two sessions per week in accordance with the guidelines of adequacy and efficiency of dialysis (16) by utilizing low-flux membrane (FR5 made by the Soha Co., Iran); then, they attended another two sessions of dialysis in the following week by utilizing the high –flux membrane (FR50, made by Soha Co., Iran).

The members of the second group were treated similarly except that they attended the dialysis with the utilization of high-flux followed by the low-flux membrane based on the guidelines of the adequacy and efficiency of dialysis provided (19). Blood samples were taken in the second dialysis session of each stage; the first sample was taken in the onset of dialysis from the arterial line (before dialysis sample) and the second sample was taken from the arterial line at the end of the dialysis session after 2 minutes and decreasing the blood flow rate to 80 mL/min (after dialysis sample). The samples were labeled and sent to the laboratory to determine the level of BUN. The lab technician was not informed about the study groups. The lab process and the technician in-charge for all samples were the same.

The urea reduction ratio (URR) and the KT/V were utilized to investigate the adequacy of dialysis. In KT/V measure, K stands for the dialyzer clearance (mL/min), T stands for the time of dialysis (min), and V, the bottom part of the fraction, is the distribution of urea, which is equal to total body water (19). To determine the adequacy of the hemodialysis based on the KT/V, the Daugirdas formula was used (SPkt/v = -Ln(R- 0.008×t) + (4+3.5R) UF). In this formula, Ln stands for the natural logarithm, R is equal to the ratio of blood urea nitrogen pre-dialysis and post-dialysis. UF is the ultrafiltration per liter and T is the time of dialysis per hour. URR is estimated based on this formula: URR = (urea pre-dialysis - urea post-dialysis)/ urea pre-dialysis x100 (20-22).

Data were collected by a questionnaire for demographic data (age, gender, interdialytic weight gain, kind of vascular access, dialysis history, etc.) and a checklist to record the BUN before and after dialysis, dialysis session time, blood flow rate, dialysate flow rate, and the ultrafiltration rate.

3.2. Ethical Considerations

The Research Council and the Human Research Ethics Committee of Hamadan University of Medical Sciences approved the study protocol and its ethical considerations (D/P/16/35/9/794). To begin the study, the researcher explained the study process to the patients, and they signed a written informed consent. The patients were also assured about data confidentiality, safeness of the study, and their right of not to participate. We also observed all ethical issues in accordance with the last version of the Helsinki Declaration.

3.3. Statistical Analysis

Data were analyzed using SPSS version 13 and descriptive statistics (frequency, percentage mean and standard deviation) and inferential statistics (t test for comparison of KT/V, URR and BUN in high-flux and low-flux membranes and paired-t test for comparison of pre-dialysis and post-dialysis BUN in high-flux and low-flux membranes).

The dialysis adequacy was classified into three groups: inadequate dialysis (KT/V ≤ 0.89, or URR ≤ 0.60); relatively adequate dialysis (KT/V = 0.90 to 1.29 or URR = 0.61 to 0.70); and the totally adequate dialysis (KT/V ≥ 1.3, or URR ≥ 0.70). Statistical significance was considered at *P* value < 0.05.

4. Results

Most of participants (67.5%) were male with the mean of 47.56 ± 10.79 years old, 87.5% of the participants used fistula for dialysis. Eighty-five percent of the participants were living in urban areas, and forty percent had dialysis history for a period of three to four years. The mean of interdialytic weight gain was 1.91 ± 1.07 kg. The blood flow rate was between 220-300 mL/min with a mean of 271 ± 18.91 mL/min (Table 1).

The mean blood urea nitrogen (BUN) before low-flux dialysis was 93.90 ± 20.51 mg/dL, which reduced at the end of the dialysis to 36.87 ± 13.16 mg/dL. The observed difference was statistically significant, (*P* < 0.001). Furthermore, the mean of the BUN before high-flux dialysis was 95.32 ± 19.69 mg/dl, which reduced to 32.35 ± 8.83 mg/dL at the end of dialysis, which was statistically significant (*P* < 0.001) (Table 2).

The mean of BUN before using the low-flux, (93.90 ± 20.51 mg/dL) and high-flux membrane (95.32 ± 19.69 mg/dL) were not significantly different (*P* = 0.725). Although the mean of BUN after high-flux dialysis (32.35 ± 8.83 mg/dL) was lower than the mean of the BUN after low-flux dialysis (36.87 ± 13.16 mg/dL), this difference was not statistically significant (*P* = 0.071) (Table 2).

The URR was 60% to 80% for half of the patients in low-flux dialysis; whereas, 70% of the patients in high-flux dialysis had the URR of 60% to 80%. The mean of URR for patients in low-flux dialysis was 0.65 ± 0.14, and in the high-flux dialysis was 0.65 ± 0.09. Although the adequacy of dialysis based on URR was higher in the high-flux dialysis, the difference was not statistically significant (*P* = 0.211) (Table 3).

In high-flux dialysis, the most frequent (32.5%) of KT/V was 1.2 to 1.4 (mean 1.27 ± 0.28); while, in low-flux dialysis the most frequent (30%) of KT/V was 1 to 1.2 (mean 1.1 ± 0.32); these differences was statistically significant (*P* = 0.017) (Table 4), which reveals the relative adequacy of high-flux dialysis.

Table 1. Characteristics of the Participants

Variables	No. (%)
Dialysis history	
≤ 2 years	10 (25)
3 - 4 years	16 (40)
≥ 5 years	14 (35)
Gender	
Male	27 (67.5)
Female	13 (32.5)
Vascular access	
Fistula	35 (87.5)
A-V graft	5 (12.5)
Citizen	
Urban	34 (85)
Rural	6 (15)
Age, y	47.56 ± 10.64 [a]
Interdialytic weight gain, kg	1.91 (1.07)
Blood flow rate, mL/min	271 (18.91)
Dialysate flow rate, mL/min	500 (10)

[a] mean ± SD.

Table 2. Comparison of Pre-dialysis and Post-dialysis BUN in High-Flux and Low-Flux Membranes

Membrane	Pre-dialysis BUN [a]	Post-dialysis BUN [a]	Paired t test
Low-Flux	93.90 ± 20.51	36.87 ± 13.16	t = 18.743, P = 0.001
High-Flux	95.32 ± 19.69	32.35 ± 8.83	t = 21.982, P = 0.001
t test	t = 0.355, P = 0.725	t = 1.859, P = 0.071	

[a] Data are presented as Mean ± SD.

Table 3. Comparison of URR in High-Flux and Low-Flux membranes [a]

URR	High-Flux	Low-Flux
0.40 - 0.59	11 (27.5)	18 (40)
0.60 - 0.79	28 (70)	20 (50)
0.80 - 0.99	1 (2.5)	2 (5)
Mean ± SD	0.65 ± 0.09	0.61 ± 0.14
Paired-t test	t = 1.262, P = 0.211	

[a] Data are presented as No. (%) and mean ± SD.

Table 4. Comparison of KT/V index in High-Flux and Low-Flux membranes [a]

KT/V	High-Flux	Low-Flux
0.60 - 0.79	3 (7.5)	6 (15)
0.80 - 0.99	4 (10)	8 (20)
1.0 - 1.19	9 (22.5)	12 (12)
1.20 - 1.39	13 (32.5)	6 (15)
1.40 - 1.59	8 (20)	4 (10)
1.60 - 1.79	1 (2.5)	4 (10)
1.80 - 1.99	1 (2.5)	0 (0)
2.0 - 2.20	1 (2.5)	0 (0)
Mean ± SD	1.27 ± 0.28	1.1 ± 0.32
Paired -t test	t = 2.434, P = 0.017	

[a] Data are presented as No. (%) and mean ± SD.

Table 5. Dialysis Adequacy Based on KT/V and URR in High-Flux and Low-Flux Membranes [a]

Dialysis Adequacy	KT/V		URR	
	High-Flux	Low-Flux	High-Flux	Low-Flux
Inadequate	5 (12.5)	9 (22.5)	11 (27.5)	17 (42.5)
Insufficient	15 (37.5)	23 (57.5)	19 (47.5)	15 (37.5)
Totally adequate	20 (50)	8 (20)	10 (25)	8 (20)
Statistical indicators	$\chi^2 = 9.839$, P = 0.043		$\chi^2 = 7.180$, P = 0.127	

[a] Data are presented as No. (%).

High-Flux dialysis was totally adequate in 50% of the cases and it was inadequate in 10% of patients based on KT/V values. The utilization of low-flux dialysis, however, showed the adequacy only in 20% of cases, and it was inadequate in the other 20%. In estimating the adequacy of dialysis based on the URR, in high-flux dialysis, 25% of participants had totally adequate dialysis and 27.5% had inadequate dialysis. While in the low-flux dialysis, only 20% of participants had totally adequate dialysis and 42.5% had insufficient adequacy of dialysis (Table 5).

5. Discussion

In the present study, the mean adequacy of dialysis by using low-flux membrane based on KT/V was 1.10 ± 0.32, which was still far from the minimum level introduced by the Office of Special Disease of the Ministry of Health of Iran (KT/V = 1.20). Hojjat investigated the adequacy of dialysis in 68 Chronic Renal Failure patients in Jahroom, Iran. His findings revealed that the measures of KT/V was less than 0.8, in 35.29% of patients and URR index was less than 65%, in 58.82% of the patients, which were both less than the required minimum level. The mean of dialysis adequacy based on KT/V was 0.963 ± 0.757, which revealed an unacceptable dialysis adequacy (23).

Moslem et al. investigated the adequacy of dialysis in Ghonabad , Iran. In this research the adequacy of both high-flux and low-flux membrane was investigated in two groups (each group 15 participants). The mean of KT/V in the high-flux group was 1.44 ± 0.32 and in 80% of the patients, the adequacy of dialysis was over 1.2 (24).

Although in this study, mean of KT/V in high-flux dialysis was more than our study (in our study 58.4% of patients had KT/V ≥ 1.2), and was not statistically different from the low-flux dialysis, in our research the adequacy was significantly better in high-flux dialysis. In Moslem et al. study, the vascular access, blood flow rate, and the type of used membrane were not mentioned. Furthermore, the size of the sample is relatively smaller than our study.

Ponikvar et al. investigated the comparative efficiency of the high-flux with low-flux membranes in patients with acute renal failure in intensive care units. The results showed no statistically significant differences in using these two membranes which could reveal the inadequacy of high-flux membrane for these patients (25). This finding may relate to the acute or chronic phase of the disease. In chronic status of renal failure due to the accumulation of waste materials, the efficiency of high-flux membranes would be obvious compared to the low-flux membranes.

El-Wakil et al. investigated the effect of high-flux versus low-flux hemodialysis on serum $ß_2$ microglobulin, advanced oxidation protein products and protein carbonyl. In the first stage, 20 patients were dialyzed by using high –flux membranes for a period of 8 weeks. In the second phase, the patients were maintained on low-flux dialysis for the same period of 8 weeks. The results revealed that the high-flux was successful in reducing the $ß_2$ microglobulin and protein carbonyl. However, the high –flux membrane did not have any observable influence on reducing the advanced oxidation protein products. In the same study, however, the use of low-flux membrane revealed all three indexes were significantly increased. The findings confirmed that the use of high-flux membrane will significantly better the diffusion of uremic toxins (22). This finding was consistent with our study.

Oates et al. investigated the effects of flux on phosphor and the responses of erythropoietin. Also, they compared the influence of high-flux and low-flux membranes in dialysis adequacy. The results showed no significant difference between the membranes (26). But, Eknoyan et al. found that high-flux membrane improves the adequacy of dialysis in chronic renal failure (27). The findings of the present research are consistent with the findings of this study.

Makar et al. compared the roles and influences of these two membranes on children hemodialysis patients. They reported no statistically significant differences in adequacy of these membranes (28). However, in our study, this difference was significantly important and provided supports for the use of high-flux membranes.

Makar et al. study was conducted with participating children who requires certain arrangements such as low blood flow rate, low dialysate flow rate and used small diameter membranes to make it tolerable for the children. These factors could have some influences on the adequacy of dialysis.

Santoro et al. investigated the effect of high-flux hemofiltration versus low-flux hemodialysis on the mortality of patients with chronic kidney failure. The results revealed that high-flux hemofiltration increased the survival and decreased in plasma $ß_2$ microglobulin level significantly (17). This study further supports the adequacy of high −flux membrane.

In another study, Mohseni and Ilali investigated the adequacy of hemodialysis using bicarbonate dialysate in Sari, Iran with 50 participants. The findings revealed that the mean of KT/V was 0.92 ± 0.26 and 86% of patients had inadequacy of dialysis (KT/V > 1.2). Furthermore, the mean of URR was 47.84% and 90% of participants (45 patients) had URR index less than the minimum standard level (65%). Because of the unacceptable quality of dialysis in most patients, they recommended periodical evaluation of the quality of dialysis as well as conducting comprehensive studies in order to determine viable methods to improve the adequacy of dialysis (29).

Malekmakan et al. found that only 32.1% of renal failure patients achieve the optimal KT/V level and have recommended using advanced dialyzers (30). In our research, however, the low-flux group revealed %35 of adequate dialysis of KT/V > 1.2 and in the high-flux group over 60% of patients had KT/V > 1.2. These findings confirm the crucial importance of high-flux membranes in achieving the requirement of optimal dialysis.

Other Iranian research findings revealed inadequacy of dialysis in most centers across the country, such as the study of Raiesifar et al. in Abadan Hemodialysis Center using low-flux membranes. The mean of KT/V was 0.9 ± 0.21 and the inadequacy of dialysis was 97.8 % (31).

Taziki and Kashi reported the inadequacy of dialysis in Sari, Iran, by using low-flux membranes and 58% of patients had KT/V less than 1 (32). Another study in Birjand, Iran, with participation of 50 patients showed that 70% of the patients had KT/V 0.9 to 1.2, and 66% of patients had URR between 61% to 70% (30). In our research, in low-flux membrane the mean of KT/V was 1.1 ± 0.32 and the ratio of inadequacy was 20%, also another 20% of the participants had KT/V less than 1, and 55% of them showed URR more than 60%. For the high-flux membrane, the mean of KT/V was 1.27 ± 0.28, and the inadequacy was seen in 10% of patients, also %17.5 of patients had KT/V less than 1, and 72% of patients had URR ≥ 60%.

The mean of KT/V in studies conducted in the USA, and Japan was 1.30 ± 0.29 and 1.30 ± 0.2, respectively (31, 32). Other studies, revealed that 60% to 80% of patients had KT/V equal to or more than 1.2 (33). These values were higher than the values in our country as presented in the literature, showing the inefficient strategies in Iranian dialysis centers. One of the reasons which significantly contributes to the observed efficiency and adequacy of dialysis in developed countries, is the more use of high-flux membranes; while, in our country mostly used low-flux membranes in dialysis centers, and the patients do not ask for them due to their unfamiliarity or carelessness.

Among the other reasons of the low quality of dialysis in Iran compared to the developed countries, are the vascular access problems (recirculation), the duration of the dialysis session, and the lack of sufficient number of dialyzers (30), the blood flow rate, the blood sampling method for determining the BUN, insufficient surface of the membranes and the type of membranes (12). Suitable setting and priming of membranes and hemodialysis set and removing the air from them as well as using high-flux membranes or low-flux membranes (with suitable size) could increase the dialysis adequacy.

The use of high −flux membranes will improve the adequacy of dialysis. Moreover, due to the characteristics of these membranes in removing the middle size and large size molecules such as $ß_2$ microglobulin, using high-flux membranes thus allows improved removal of a wider spectrum of uremic toxins which may improve the quality of life of patients on chronic hemodialysis. According to the result of this study, using these high-flux membranes in other dialysis centers is recommended.

The limitation of study was its short duration follow-up. It is recommended that further studies on comparison of high-flux and low-flux membranes be performed in longer periods.(34-36)

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Authors' Contributions

Study conception and design: Khodayar Oshvandi, Sayed Reza Borzuo, and Mahmoud Gholyaf; Data collection: Rasol Kavyannejad; and Manuscript draft and critical revision: Khodayar Oshvandi.

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